AR201-13219-B

1. **General Information**

CAS Number: 110-43-o
Name: 2-Heptanone
Methyl n-Amyl Ketone
Methyl pentyl ketone
Butyl acetone
n-Pentyl methyl ketone
MAK

II. Physical-Chemical Data

A. Melting Point

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Melting point value:	-35.5 °C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Lide, D.R. (Ed.). CRC Handbook of Chemistry and Physics. 73rd ed. Boca Raton, FL: CRC Press Inc., 1992- 1993.
Other	Last revision date: 19990921

B. Boiling Point

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Boiling point value:	151.5 °C
Pressure:	760 mmHg
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Budavari, S. (Ed.). The Merck Index – Encyclopedia of Chemicals, Drugs and Biologicals. Rahway, NJ: Merck and Co., Inc 1989, 737
Other	Last revision date: 19990921

C. Vapor Pressure

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Vapor pressure value:	1.6 – 3.86 mmHg
Temperature:	25 °C
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Sunshine, I. (Ed.). CRC Handbook of Analytical Toxicology. Cleveland: The Chemical Rubber Co., 1969, 633. Riddick, J.A., *et al*.; Organic Solvents 4th ed. NY: Wiley Interscience, (1986)
Other	Last revision date: 19990921

D. Partition Coefficient

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Log K_{OW}:	1.98
Temperature:	Unknown
Remarks:	
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Hansch, C., Leo, A.J.; Medchem Project Issue No. 26 Claremont, CA: Pomona College 1985
Other	Last revision date: 19990921

E. Water Solubility

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not specified
GLP:	Unknown
Year:	Unknown
Remarks:	
Results	
Value:	4300 mg/L
Temperature:	25^{o} C
Description:	Slight (1-10 g/L)
Remarks:	The same solubility value was indicated in two different references within HSDB. Temperature was not given with reference (1), but was listed as 25^{o} C in reference (2).
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	(1) Kirk-Othmer Encyclopedia of Chemical Technology. 3rd Ed., Volumes 1-26. New York, NY: John Wiley and Sons, 1978-1984 V13 p. 896 (1981) (2) Riddick, J.A., *et al*.; Organic Solvents 4th ed. NY: Wiley Interscience, (1986)
Other	Last revision date: 19990921

III. Environmental Fate Endpoints

A. Photodegradation

Test Substance	
Test substance:	MAK
Remarks:	Purity was reported as >99%
Method	
Method:	Flash Photolysis Resonance Fluorescence (FPRP)
Test type:	Hydroxyl radical reaction
GLP:	No
Year:	Unknown (Study was published in 1987)
Remarks:	Hydroxyl radicals were produced by the vacuum ultraviolet photolysis of water at –0.1 Torr. Following production, radicals were monitored as a function of time by the fluorescence excited by a microwave powered OH resonance lamp. Hydroxyl radical concentration was between 10^{10} and 10^{11} molecules /cm^3. This level was deemed high enough to assure pseudo-first-order kinetics with respect to radical decay.
Results	
Rate Constant:	8.67 x 10^{-11} cm^3/molecule-second
Temperature ^oC:	23 ^oC
Half-life:	4.5 hours (based on an average atmospheric hydroxyl radical concentration of 5 x 10^5 molecules/cm^3)
Remarks:	
Conclusions	Material is expected to rapidly degrade in the atmosphere.
Data Quality	
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122
References	Wallington, T.J. and Kurylo, M.J. (1987). Flash Photolysis Resonance Fluorescence Investigation of the Gas-Phase Reaction of OH Radicals with a Series of Aliphatic Ketones over the Temperature Range 240-440 K. *J. Phys. Chem.* **91,** 5050-5054.
Other	Last revision date: 19990921

B. Stability in Water

Reactivity of Selected Ketones With Water

This report has been prepared Dr. Paul Worsham of Eastman Chemical to document the known chemistry relevant to the stability of selected ketones in aqueous solution. The specific ketones addressed in this document are methyl propyl ketone (MPK; CAS# 107879), methyl isopropyl ketone (MIPK; CAS# 563804), methyl isoamyl ketone (MIAK; CAS# 110123), and methyl n-amyl ketone (MAK; CAS#110430).

Of particular concern in the evaluation of the stability of organic compounds in aqueous solution is the potential for hydrolysis. Hydrolysis is the reaction between water and an organic substrate resulting in the cleavage of existing chemical bonds and subsequent or simultaneous formation of new chemical bonds to form a different chemical compound. Typically, hydrolysis reactions involve incorporation of a water molecule into the structure of the reaction products. For organic substances that participate in hydrolysis reactions, various kinetic methods can be used to monitor the changes in concentration of reactants and determine the rate of transformation of the original substrate into reaction products. OECD Guideline 111 describes one such procedure for measuring the hydrolysis rate of water-soluble substrates as a function of pH. Substrates that exhibit high rates of hydrolysis are considered unstable in an aqueous environment.

Ketones as a class, and specifically the ketones identified above, do not participate in hydrolysis reactions. These ketones do not possess labile leaving groups that can be displaced by the nucleophilic attack of a water molecule, as is required in the mechanism of many hydrolysis reactions. Thus, it would not be meaningful to attempt to measure a hydrolysis rate using a protocol such as OECD Guideline 111.

Certain ketones may add water to form a hydrate under aqueous conditions, especially in the presence of mild acid; but, this addition is an equilibrium reaction that is reversible upon a change in water concentration, and the reaction ultimately leads to no permanent change in the structure of the ketone substrate.[1,2]

A significant property of most ketones is that the hydrogen atoms on the carbons next to the carbonyl group are relatively acidic when compared to hydrogen atoms in typical hydrocarbons. Under strongly basic conditions these hydrogen atoms may be abstracted to form an enolate anion. This property allows ketones, especially methyl ketones such as the four ketones above, to participate in condensation reactions with other ketones and aldehydes. This reaction is called an aldol reaction and generates a higher molecular weight ketone having a hydroxyl group at the site of attack by the enolate anion. This type of condensation reaction is favored by high substrate concentrations and high pH (greater than 1 wt% NaOH). It is conceivable that some alkyl ketones, especially methyl ketones, could participate in aldol reactions in dilute aqueous solution at pH of 9 or higher. But, these reactions would be expected to be slow at ambient temperature, and the equilibrium for condensation of two ketones is unfavorable for aldol product formation[3]. Also, formation of the aldol product is reversible unless dehydration of the aldol occurs. Dehydration of an aldol intermediate in aqueous solution at ambient temperature also would be very slow.

Based on the properties of ketones described above one must conclude that MPK, MIPK, MIAK, and MAK are not subject to hydrolysis, but may participate in other transformations that convert the ketone to higher molecular weight compounds. These reactions would be expected to be very slow at mild temperatures and moderate pH. Therefore, it is my conclusion that MPK, MIPK, MIAK, and MAK should be considered stable in aqueous solution at temperatures and pH levels relevant to environmental and human exposure.

References:

(1) Bell and Clunie, *Trans. Faraday Soc.*, **48,** 439, (1952).
(2) Cohn and Urey, *J. Am. Chem. Soc.*, **60**, 679 (1938).
(3) March, J., ed. "Advanced Organic Chemistry", 3rd edition, p. 831, John Wiley & Sons, New York, 1985.

C. Biodegradation

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.7%
Method	
Method:	Method C.6., "Degradation, Chemical Oxygen Demand", Official Journal of the European Communities, No. L383A/227, 29 December 1992.
Test type:	Chemical Oxygen Demand (COD)
GLP:	Yes
Year:	1997
Remarks:	
Results	
Results:	2.42 grams COD/gram of test substance
Remarks:	The value is a mean of three replicates.
Conclusions	
Data Quality	
Remarks:	This was a well-documented study that followed established guidelines and was conducted under GLP assurances.
References	Chemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services Division, Eastman Kodak Company, Rochester, NY; Report No. COD-00590. July 24, 1997.
Other	

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.7%
Method	
Method:	Method C.5., "Degradation, Biochemical Oxygen Demand", Official Journal of the European Communities, No. L251/212, 19.9.84. Method is similar to OECD: TG-301C: Modified MITI Test.
Test type:	Biochemical Oxygen Demand (BOD)
GLP:	Yes
Year:	1997
Remarks:	BOD was determined after 5 and 20 days. The 20-day value was performed in duplicate.
Results	
Results:	BOD5 was 1.77 grams BOD/gram of test substance BOD20 was 2.00 grams BOD/gram of test substance
Remarks:	The BOD 20 value was a mean of two replicates.
Conclusions	The test material is considered to be "Readily Biodegradable" based on a BOD5/COD ratio greater than 0.5 (1.77/2.42 = 0.73)
Data Quality	
Remarks:	This was a well-documented study that followed established guidelines and was conducted under GLP assurances.
References	Biochemical Oxygen Demand Determination; Environmental Analytical Services, Chemicals Quality Services Division, Eastman Kodak Company, Rochester, NY; Report No. COD-00589. July 24, 1997.
Other	

D. Transport between Environmental Compartments (Fugacity)

Test Substance	
Test substance:	MAK
Remarks:	
Method	
Test type:	Estimation
Model used:	Level III Fugacity Model; EPIWIN: EQC from Syracuse Research Corporation
Remarks:	
Results	
Model data and results:	Concentration (%)
Estimated distribution and media concentration (levels II/III):	Air 5.97 Water 39.4 Soil 54.6 Sediment 0.0724
Remarks:	Physical chemical values utilized in this model were default values obtained from the EPIWIN program.
Data Quality	
Remarks:	
References	Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 1.2, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay *et al*. 1996; *Environ. Toxicol. Chem.* **15(9)**, 1618-1626 and *Environ. Toxicol. Chem.* **15(9)**, 1627-1637.
Other	

IV. Ecotoxicity

A. Acute Toxicity to Fish

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Not Specified
Test type:	Flow-through
GLP:	Unknown
Year:	Unknown
Species/strain:	Fathead minnow (*Pimephales promelas*)
Analytical monitoring:	Dissolved oxygen 7.2 mg/L, hardness 46.4 mg/L, alkalinity 42.1 mg/L, pH 7.72, and temperature 24.2 ^{o}C.
Exposure period:	96-hr
Remarks:	
Results	
Endpoint value:	LC_{50} 131 mg/L (confidence limit 126 –137 mg/l); EC_{50} 128 mg/L
Remarks:	
Conclusions	The LC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Data obtained from Hazardous Substances Data Bank Number: 1122 and were noted to have been peer reviewed. However, no raw data were available for review.
References	Geiger D.L., Poirier S.H., Brooke L.T., Call D.J., eds. Acute Toxicities of Organic Chemicals to Fathead Minnows (*Pimephales Promelas*). Vol. III. Superior, Wisconsin: University of Wisconsin-Superior, 1986. 179
Other	Last revision date: 19990921

B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-202 and EEC/Annex V C.2
Test type:	Acute immobilization
GLP:	Yes
Year:	1998
Species/strain:	*Daphnia magna*
Analytical monitoring:	Aliquots of exposure solution were submitted for concentration determinations at 0, 24, and 48 hours. Temperature, dissolved oxygen, and pH were also determined at these same time periods.
Test details:	48-hour exposure period; semi-static
Remarks:	No protocol deviations were noted. Study was conducted in duplicate and results were averaged.
Results	
Nominal concentration:	6.25, 12.5, 25, 50, and 100 mg/L
Measured concentration:	6.46, 13.01, 24.52, 47.86, 90.10 mg/L
Endpoint value:	EC_{50} > 90.10 mg/L
Biological observations:	The behavior of all *Daphnia* was comparable to controls.
Statistical methods:	NA (no effects were seen at highest exposure concentration)
Remarks:	Water temp ranged from 19 to 21 ^{o}C, pH ranged from 8.2 to 8.7, and dissolved oxygen ranged from 8.6 to 9.3 mg/L.
Conclusions	The 48-hour EC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	An Acute Aquatic Effects Test with the Daphnid; Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-431-902185-A; June 15, 1998
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-201
Test type:	Growth inhibition of algae
GLP:	Yes
Year:	1998
Species/strain:	*Selenastrum capricornutum*
Endpoint basis:	Cell concentrations (biomass) and growth rate
Exposure period:	72-hours
Analytical procedures:	Temperature, light intensity, rpm, and test substance concentration were assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours.
Remarks:	
Results	
Nominal concentration:	12.5, 25, 50, 100, and 200 mg/L
Measured concentration:	6.2, 11.9, 22.1, 42.7, 86.3 mg/L (geometric mean)
Endpoint value:	The estimated E_bC_{50} (0-72 hr) was 75.5 mg/L; the E_rC_{50} (0-72 hr) was 98.2 mg/L
NOEC, LOEC, or NOEL, LOEL:	The 72 hr NOEC was estimated to be 42.7 mg/L
Biological observations:	No deformed cells were noted
Was control response satisfactory:	Yes (culture concentrations increased by a factor of 136-fold)
Statistical methods:	EC_{50} and NOEC values were determined through use of SAS statistical software program AL_ACUTE (Ver. 2.2).
Remarks:	A mean illumination of 741 +/- 1.7 foot-candles was maintained. The mean temperature was 24°C and pH ranged from 7.3 to 7.7. Cultures were oscillated at 100 rpm. The significant loss (up to 82% over the course of the study) in test material was attributed to volatilization. No protocol deviations were noted.
Conclusions	The 72-hour E_bC_{50} and E_rC_{50} values indicate that, based on this study, the test substance would be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would be classified in a "moderate concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	A Growth Inhibition Test with the Alga, *Selenastrum capricornutum*; Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-512-902185-B; October 13, 1998
Other	

V. Toxicological Data

A. Acute Toxicity

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LD_{50} estimate
GLP:	No (Pre-GLP)
Year:	1964
Species/strain:	Rat/unknown
Sex:	Unknown
Animals/sex/dose:	10 animals in total were used
Vehicle:	Material was administered undiluted
Route of exposure:	Oral
Remarks:	Rats were administered doses of MAK ranging from 200-3200 mg/kg. Animals were monitored for clinical observations and weight change for 14-days.
Results	
Value:	LD_{50} = 1600 mg/kg
Deaths at each dose:	Report only indicated deaths occurring at 1600 mg/kg on day 1 after 5 hours
Remarks:	Clinical signs of toxicity included slight to very weak, prostration, vasodilatation, labored breathing, and ataxia. Except for labored breathing, which was noted at doses of 800 mg/kg and above, clinical signs at specific dose levels were not indicated. Autopsy was negative.
Conclusions	Material is considered slightly toxic
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Basic data are given.
References	Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 64-164; May 1, 1964.
Other	

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LD_{50} estimate
GLP:	No (Pre-GLP)
Year:	1964
Species/strain:	Mouse/unknown
Sex:	Unknown
Animals/sex/dose:	6 animals in total
Vehicle:	Material was administered undiluted
Route of exposure:	Oral
Remarks:	A total of 6 mice were administered doses of MAK ranging from 400-1600 mg/kg. They were monitored for clinical observations and weight change for 14-days.
Results	
Value:	LD_{50} = 1600 mg/kg
Deaths at each dose:	No deaths were noted at any dose
Remarks:	Animal appearance was noted as normal to quite weak.
Conclusions	Material is considered slightly toxic
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Basic data are given.
References	Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 64-164; May 1, 1964.
Other	

Test Substance	
Test substance:	MAK
Remarks:	Purity unknown
Method	
Method:	Acute lethality; Other
Test type:	LC_{50} estimate
GLP:	No (Pre-GLP)
Year:	1964
Species/strain:	Rat/unknown
Sex:	Unknown
Animals/sex/dose:	3 animals/exposure level
Vehicle:	None
Route of exposure:	Inhalation, whole-body
Remarks:	Rats were exposed to MAK in whole-body chambers for 4 hours at 5,126 ppm, and 6 hours at 4,169, 832, 1,437, and 2,016 ppm. It was noted that the inhalation chambers were maintained at 24 ^{o}C. Animals were monitored for clinical observations and weight change for 14-days.
Results	
Value:	LC_{50} 2000-4000 ppm (6-hr)
Deaths at each dose:	At 5,126 ppm all 3 animals died shortly after their 4-hour exposure. At 4,169 ppm, 1/3 died after 4 hours and the other 2 died shortly after their 6-hour exposure ended. No deaths were noted at 2,016 ppm or lower. Clinical signs in all studies included piloerection, vasodilatation, hypernea, lassitude, ataxia, and prostration. All animals gained weight, although higher-dosed animals gained less.
Remarks:	
Conclusions	
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Basic data are given.
References	Laboratory of Industrial Medicine, Eastman Kodak Company. Rochester, NY. Reference No. 64-164; May 1, 1964.
Other	

B. Repeated Dose Toxicity

Test Substance	
Test substance:	MAK
Remarks:	Purity was 97%
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No (Pre-GLP)
Year:	Unknown (studies were published in 1978, 79, and 81)
Species/strain:	Rat/Sprague-Dawley and Primate/*Macaca fascicularis*
Route of exposure:	Inhalation
Duration of test:	10-months
Exposure levels:	100 and 1000 ppm
Sex:	Males
Exposure period:	6 hours/day
Frequency of treatment:	5 days/week
Control group and treatment:	Controls were exposed to room air.
Post-exposure observation period:	None
Remarks:	Groups of 50 rats and 8 monkeys were randomly assigned to each of the three exposure groups. Animals were exposed using whole-body chambers. At necropsy, lungs, liver, heart, spleen, kidney, adrenals, pancreas, testes, brain, and sciatic nerve were harvested for microscopic examinations. Clinical chemistries were conducted in primates after 1, 3, and 6 months of exposure and at study termination. Blood and urine was collected from both species at termination for metabolite identification. Liver microsomal enzyme induction was evaluated in rodents by assessing barbiturate-induced sleeping times. Rats also had tissue distribution analyses conducted following both ip (10 mg/kg) and inhalation exposure to [^{14}C]MAK. Tissues, urine and feces were collected 2, 4, 8, 12, 24, 48, and 72 hours after administration of the radiolabeled MAK. Distribution and excretion was assessed in both naive and pre-exposed animals. At monthly intervals both species were evaluated for neurological function by assessing maximum motor-nerve conduction velocity (MCV) of the sciatic and ulnar nerves and amplitude of evoked muscle action potential (MAP). Primates also under went electroencephalograms (EEG) and had visually evoked action potential recorded. Cardiopulmonary studies, including mechanical properties (compliance and resistance), lung volumes, flow-volume dynamics, distribution of ventilation, diffusion, and gas exchange were conducted on monkeys at the start of the study and after 6 months of exposures. Electrocardiographic (ECG) examinations were also conducted at the time of pulmonary function testing.

Results	
NOAEL (NOEL):	1025 ppm (both species)
Actual exposure levels:	131 +/-30 ppm and 1025 +/- 136 ppm
Toxic responses by dose:	Both species tolerated the exposures without developing overt signs of toxicity or alterations in weight gains or clinical chemistries. There was no effect on barbiturate sleeping times. Neither species exhibited any gross or microscopic changes in any organ or tissue examined. Six months of exposure did not alter the overall cardiopulmonary function, EEG and ECG readings, or induce any evidence of neurotoxicity. MAK was detected in the serum and urine from both species at both exposure levels. While methyl n-amyl alcohol was detected only in the urine and serum from high dose primates. Although some significant post-MAK peaks were observed, they were not identified by GC/MS. They were present in 4/14 low dose animals and 10/12 receiving 1025 ppm exposures. Regardless of the route of administration, i.e., ip or inhalation, or whether animals were naive or had been pre-exposed, the liver contained the most radioactivity. The next highest levels were detected in the kidney, pancreas, and lungs. The brain contained some of the lowest amounts. Excretion of MAK into the urine and feces peaked at 12 hours and remained relatively constant through 48-hours. Fecal excretion through 72-hours only accounted for 2% of the administered dose.
Statistical methods:	Multivariate analysis of covariance (MANOVA), Kruskial-Wallis test, and Student's t test.
Remarks:	
Conclusions	Animals appeared to tolerate exposure to MAK with minimal effects.
Data Quality	
Reliability:	Reliable with restriction
Remarks:	This appears to be a very robust and well-conducted study; however, basic data are not available for review.
References	1. Lynch, D.W., Lewis, T.R., Moorman, W.J., Plotnick, H.B., Schuler, R.L., Smallwood, A.W., and Kommineni, C. Inhalation Toxicity or Methyl n-Amyl Ketone (2-Heptanone) in Rats and Monkeys. *Toxicology and Applied Pharmacology* **58,** 341–352, 1981. 2. Johnson, B.L., Setzer, J.V., Lewis, T.R., and Hornung, R.W. An Electrodiagnostic Study of the Neurotoxicity of Methyl N-Amyl Ketone. *American Industrial Hygiene Association* **39,** 866–872, 1978. 3. Johnson, B.L., Anger, W.K., Setzer, J.V., Lynch, D.W., and Lewis, T.R. Neurobehavioral Effects of Methyl N-Butyl Ketone and Methyl N-Amyl Ketone in Rats and Monkeys: A Summary of NIOSH Investigations. *Journal of Environmental Pathology and Toxicology* **2,** 113–133, 1979.
Other	This study was conducted by The National Institute for Occupational Safety and Health, Division of Biomedical and Behavioral Science in Cincinnati, OH.

Test Substance	
Test substance:	MAK
Remarks:	Purity was 98% at minimum
Method	
Method:	Other
Test type:	Repeated exposure
GLP:	No (Pre-GLP)
Year:	Unknown (studies were published in 1972)
Species/strain:	Rat/CFE
Route of exposure:	Oral gavage
Duration of test:	13-weeks
Dose levels:	0, 20, 100, and 500 mg/kg
Sex:	Male and Female; 15/dose level
Frequency of treatment:	A single daily gavage
Control group and treatment:	Yes; Corn oil
Post-exposure observation period:	None
Remarks:	An additional 5 animals/sex receiving 100 and 500 mg/kg were terminated after 2 and 6 weeks of dosing. All animals were assessed for body weight, food and water intakes, clinical chemistries, hematology, and urinalysis. At termination, animals underwent a gross examination with 12 different organs harvested to assess changes in weight and 23 different tissues were preserved for microscopic analysis.
Results	
NOAEL (NOEL):	20 mg/kg (NOEL)
Toxic responses by dose:	No alterations were noted in appearance, behavior, or body weight gains. No statistically significant changes from control were noted in hematology, serum chemistries, or urinary parameters. However, an increase in urine cellularity was noted in males at the mid- and high-dose levels after 13 weeks and in the high-dose group after 6 weeks. Changes in relative organ weights were noted in the liver of both sexes at the high dose at Week-13 and in males only after 6 weeks (high dose) and at 2 weeks (high and mid). Significant alterations were also seen after 13 weeks in relative kidney weight in mid and high dose males. Other organs exhibiting weight changes were not significant when corrected for body weight. Despite the reported organ weight changes, no histological alterations were noted in any tissue. No serum biochemical changes were noted that might also be reflective of renal or hepatic toxicity.
Statistical methods:	Data present in graphs and figures were noted to have been compared using Student's t test.
Remarks:	
Conclusions	
	The effect in the liver was likely an adaptive response from continual exposure to large doses of test material. The increased urine cellularity was only noted in males and as not accompanied by any alterations in the histological appearance of the kidney or urinary bladder.

Data Quality	
Reliability:	Reliable with restriction
Remarks:	Acceptable, well-documented publication that meets scientific principles. Study was conducted by the British Industrial Biological Research association
References	Gaunt, I.F., Carpanini, F.M.B., Wright, M.G., Grasso, P., Gangolli, S.D. (1972) Short-term Toxicity of Methyl Amyl Ketone in Rats. *Food Cosmet. Toxicology* **10,** 625–636.
Other	

C. Genetic Toxicity - Mutation

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99%
Method	
Method:	OECD: TG-471
Test type:	*In vitro* mutagenicity
GLP:	Yes
Year:	1994
Species/strain:	*Salmonella typhimurium*/TA98, 100, 1535, 1537, 1538
Metabolic activation:	Yes; Aroclor 1254-induced SD rat liver S9
Concentration tested:	Maximum concentration tested was 5000 ug/plate
Remarks:	Positive controls (2-aminoanthracene, 2-nitrofluorene, sodium azide, 9-aminoacridine) were run concurrently. Negative control was the test vehicle dimethylsulfoxide. Test material as evaluated in triplicate at each dose level.
Results	
Result:	No positive responses were induced in any of the tester strains
Cytotoxic concentration:	>5000 ug/plate
Precipitation concentration:	No precipitate was observed at 5000 ug/plate
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Means and standard deviation were determined for each of the dosing regimens; Further statistical analyses were not needed due to the absence of an increase in the number of revertants colonies at any dose beyond the positive control.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD-like guideline study conducted under GLP assurances.
References	Ames mutagenicity study of methyl n-amyl ketone. Microbiological Associates Inc., Rockville, MD; Sponsor Project Number STP-195; Laboratory Study Number G94BJ71.501; December 15, 1994.
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance	
Test substance:	MAK
Remarks:	Purity was 99.8%
Method	
Method:	OECD: TG-473
Test type:	*In vitro* mammalian chromosomal aberrations assay
GLP:	Yes
Year:	1998
Species/strain:	Chinese hamster ovary cells (CHO)
Concentrations tested:	Up to 1200 ug/ml (this level exceeds the 10 mM max. recommended level)
Metabolic Activation:	Aroclor 1254-induced SD rat liver S9
Remarks:	The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was the test vehicle dimethylsulfoxide.
Results	
Result:	No significant increases in cells with chromosomal aberrations, polyploidy, or endoreduplication were observed on analyzed cultures.
Cytotoxic concentration:	>1200 ug/ml (no evidence of cytotoxicity was seen)
Precipitation concentration:	No precipitate was observed at maximum concentration tested.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Statistical analysis employed a Cochran-Armitage test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances
References	Covance Laboratories Inc., Vienna, VA; Study number: 19226-0-437OECD; June 18, 1998
Other	

E. Developmental Toxicity

Test Substance	
Test substance:	MAK
Remarks:	Purity was >99%
Method	
Method:	OECD: TG-421
GLP:	Yes
Year:	1996
Species/strain:	Rats/Sprague-Dawley
Sex:	Male and Female (12/exposure level)
Route of exposure:	Inhalation, whole-body
Exposure levels:	0, 80, 400, and 1000 ppm
Actual exposure levels:	0, 78.6, 405.8, and 1022.6 ppm
Exposure period:	6 hrs/day
Frequency of treatment:	7 days/week
Control group and treatment:	Controls were exposed to filtered room air and housed similarly
Duration of test:	Males were exposed for 50 days while females were exposed for 34 to 47 days
Remarks:	
Results	
Maternal toxicity NOEL:	80 ppm NOEL
Repro./Develop. toxicity NOEL:	1000 ppm NOEL
Parental toxic responses:	There were no mortalities. A dose responsive reduction in activity was noted during the exposure period in the high- and mid-dose animals only. Animals appeared to become acclimated as this reduction went from moderate, to minor, to minimal by study conclusion. Males in the high dose group exhibited a decrease in food consumption during the days 0-7 only. There was no effect on body weight in either sex, although mid-dose females exhibited less of a weight change during days 0-7 of gestation. There were no effects noted in any of the litter parameters due to MAK exposure (reproductive performance, gestation length, number of live/dead pups, implant total, prenatal loss, % survival, ratio of male/female pups, or pup weight). There were no effects noted in either sex on any of the selected organs that were weighed, or examined grossly or histologically.
Fetal toxic responses dose:	There were no treatment-induced changes in pup clinical signs or abnormalities, or weight gains at any measured time-period.
Statistical Methods:	Homogeneity of data was evaluated using Bartlett's test (p ? 0.01), one-way analysis of variance (ANOVA) (p ? 0.05), and Dunnett's t-test (p ? 0.05) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test (p ? 0.01), the data were evaluated using a Kruskal-Wallis H-test (p ? 0.05) followed by Mann-Whitney U-test (p ? 0.05). The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test (p ? 0.05). The total number of pups per litter (live and dead) and the total number of live pups per litter were evaluated using a linear regression model (p ? 0.05).
Remarks:	
Conclusions	Test material did not induce reproductive or developmental toxicity under the conditions of this assay.

Data Quality	
Reliability:	Reliable without restriction
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study Number HAEL 95-0202; October 7, 1996.
Other	

F. Toxicity to Reproduction

See robust summary E above which was a combined developmental/reproductive toxicity screening assessment.